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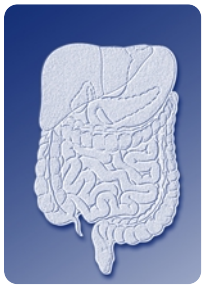
The State of the Art in the Management of Inflammatory Bowel Disease



A CASE STUDIES NEWSLETTER SERIES

The fourth in a series of educational newsletters based in part on the proceedings of a roundtable.

PRESENTED BY:

The Office on Women's Health
of the
U.S. Department of Health and Human Services
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SOCIETY FOR WOMEN'S HEALTH RESEARCH

IN COOPERATION WITH:

Crohn's & Colitis Foundation of America

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and Clinical Pharmacology
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and Nutrition
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Chicago, Illinois

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Faculty

Maria T. Abreu, MD 13, 42
Director, Basic and Translational Research
IBD Center
Cedars-Sinai Medical Center
Los Angeles, California

Theodore M. Bayless, MD 13, 42, 53
Professor of Medicine
Johns Hopkins University School of Medicine
Director, Meyerhoff IBD Center
Johns Hopkins Hospital
Baltimore, Maryland

Charles N. Bernstein, MD 3, 5, 9, 16, 42, 49
Professor of Medicine
University of Manitoba
Inflammatory Bowel Disease
Clinical and Research Centre
Winnipeg, Manitoba, Canada

Judy Cho, MD *
Assistant Professor of Medicine
University of Chicago
Chicago, Illinois

Robynne Chutkan, MD *
Assistant Professor of Medicine
Georgetown University Medical Center
Washington, DC

Bess Dawson-Hughes, MD 19, 34, 42, 44
Professor of Medicine
Chief, Calcium and Bone Metabolism Laboratory
US Department of Agriculture Human Nutrition
Research Center on Aging
Tufts University
Boston, Massachusetts

Victor W. Fazio, MD *
Rupert B. Turnbull Professor and Chair
Chairman, Department of Colorectal Surgery
Co-Chairman, Digestive Disease Center
Cleveland Clinic Foundation
Cleveland, Ohio

Susan Galandiuk, MD 1, 4, 28, 30, 32,
Professor of Surgery, Program Director 40, 41, 47, 52
Section of Colon and Rectal Surgery
Department of Surgery, University of Louisville
Louisville, Kentucky

Stephen B. Hanauer, MD 4, 13, 42, 45
Professor of Medicine and Clinical Pharmacology
Director, Section of Gastroenterology and Nutrition
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

E. Jan Irvine, MD 8, 22, 39, 42
Professor of Medicine
Division of Gastroenterology
McMaster University
Hamilton, Ontario, Canada

Stephen P. James, MD *
Deputy Director
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive
and Kidney Diseases
Bethesda, Maryland

Sunanda V. Kane, MD 4, 13, 27, 42
Assistant Professor of Medicine
University of Chicago
Chicago, Illinois

Seymour Katz, MD 4, 13, 39, 42
Clinical Professor of Medicine
New York University School of Medicine
North Shore University Hospital
Long Island Jewish Health Systems
St. Francis Hospital
Great Neck, New York

James F. Marion, MD 13, 42
Assistant Clinical Professor of Medicine
Mount Sinai School of Medicine
New York, New York

Lloyd Mayer, MD 13, 37
Professor and Chairman
Immunobiology Center
Mount Sinai School of Medicine
New York, New York

Daniel H. Present, MD 10, 12, 13, 15, 17, 21, 25,
Clinical Professor of Medicine 28, 31, 33, 42, 43, 44,
Mount Sinai Medical Center 45, 46, 50, 53, 54
New York, New York

Robert H. Riddell, MD 34
Professor of Pathobiology and Laboratory Medicine
Mount Sinai Hospital
Toronto, Ontario, Canada

David B. Sachar, MD 4, 42, 43, 54
Clinical Professor of Medicine and
Director Emeritus
Gastroenterology Division
Mount Sinai School of Medicine
New York, New York

William J. Sandborn, MD 2, 4, 6, 7,
Head, Inflammatory Bowel Disease Research 11, 12, 13,
Director, IBD Clinical Research Unit 18, 20, 23,
Mayo Clinic 24, 25, 28, 29,
Professor of Medicine 30, 32, 35,36,
Mayo Medical School 40, 42,43, 45,
Rochester, Minnesota 48, 51, 55, 56

Ernest Seidman, MD 26, 38, 42, 43
CCFC/CIHR IBD Research Chair
Chief, Division of Gastroenterology,
Hepatology and Nutrition
Professor, Department of Pediatrics
University of Montreal
Montreal, Quebec, Canada

Charles A. Sninsky, MD 13, 42, 53, 54
Digestive Disease Associates
Gainesville, Florida

Christina Surawicz, MD 4
Professor of Medicine
University of Washington School of Medicine
Section Chief, Gastroenterology
Harborview Medical Center
Seattle, Washington

Douglas C. Wolf, MD *
Atlanta Gastroenterology Associates
Clinical Assistant Professor of Medicine
Emory University School of Medicine
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Associate Professor of Medicine
Harvard Medical School
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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE: A CASE STUDIES NEWSLETTER SERIES

INTRODUCTION

This newsletter presents 4 clinical scenarios that comprise frequent challenges to the gastroenterologist. The diagnostic approach will be explored for 2 patients, a woman whose diagnosis is ulcerative colitis (UC) and a child whose evaluation will reveal Crohn's disease (CD). All cases will explore treatment strategies for inducing and maintaining remission at initial presentation. As several of these cases evolve, relapse occurs, and the treatment options for patients who require more intensive therapy because of disease progression will be addressed. Finally, the lifelong course of IBD and its impact on childhood and pregnancy are the focus of 2 cases, which highlight the special considerations and needs that are essential elements in an overall approach to patient care. The cases are as follows:

- A 24-year-old woman presents with persistent bloody diarrhea, abdominal cramps, fever, and weight loss. How would you treat this patient through diagnostic workup, induction, and maintenance therapy?
- You suspect IBD in an 11-year-old boy who presented with upper abdominal pain, fever, weight loss, and slowed growth rate. What diagnostic workup and treatment are appropriate for this patient?
- A 29-year-old woman with Crohn's ileitis, successfully maintained on mesalamine, discovers she is pregnant. How should she be counseled regarding treatment during pregnancy and breast-feeding?
- A 30-year-old man (an ex-smoker) with a 3-year history of pancolitis achieved remission following a 9-week course of corticosteroids. What are the treatment options for maintenance therapy?

LEARNING OBJECTIVES

After completing this program, participants should be able to summarize and explain

- Current inductive and maintenance therapies for mildly to moderately active distal ulcerative colitis
- Current approaches to treatment of relapse and progression of mild ulcerative colitis
- The diagnosis, treatment, and special considerations in the management of Crohn's disease in children
- Treatment options and issues in the induction and maintenance of remission in patients with Crohn's disease who are pregnant or breast-feeding
- Treatment options for relapse in severe, extensive ulcerative colitis

A 24-year-old woman presents with persistent bloody diarrhea, abdominal cramps, fever, and weight loss. What is your diagnostic approach for this patient?

The first priority in the care of any patient presenting with bloody diarrhea is to determine the diagnosis, which is reached through a combination of clinical, laboratory, endoscopic, histologic, and radiographic evaluations. Findings from these examinations usually will allow distinction between UC, CD, and the disorders that mimic them, including colitis caused by infectious agents or drugs (such as nonsteroidal anti-inflammatory drugs), vasculitis, diverticulitis, or neoplasms.

Although they share a number of epidemiologic, pathophysiologic, and clinical features, UC and CD are considered distinct diseases. However, for 10% to 20% of patients presenting with colitis, specific differentiation between UC and CD will not be possible initially, with a resulting diagnosis of "indeterminate colitis."[2] A family history of IBD should be explored with the patient, because a family occurrence is found in both UC (in 10% to 25% of patients) and CD (20% to 40% of patients).[2] Smoking history also may be relevant: UC patients are more likely to be former smokers or nonsmokers, and CD patients are more likely to be current smokers.[2] Common presenting symptoms in UC are bloody stools with mucus and diarrhea and abdominal cramping, occasionally associated with weight loss and fever. Systemic symptoms are more frequent in CD than in UC and include abdominal pain and tenderness, chronic or nocturnal diarrhea, malaise, weight loss, and fever.[2]

Physical examination of patients with UC may reveal only diffuse abdominal tenderness. In CD, patients with ileocecal disease may have tender abdominal masses and abdominal distention.[2] Extraintestinal

manifestations may be present; some are more suggestive of UC and some of CD.[3] External anal tags, perianal abscesses, and gluteal or rectovaginal fistulae are associated with CD; in most patients with UC, the perianal region appears normal.[2,4]

Laboratory analysis includes a complete blood count and differential, prothrombin time, electrolyte levels, blood urea nitrogen, creatinine, liver enzyme levels, erythrocyte sedimentation rate (ESR), C-reactive protein level, and stool examination for pathogens.[4] Anemia, leukocytosis, thrombocytosis, and elevated ESR or C-reactive protein occur in both UC and CD.[2] Serologic testing (particularly combined perinuclear antineutrophil cytoplasmic antibody [pANCA] for UC and anti-*Saccharomyces cerevisiae* antibody [ASCA] for CD) may be useful in differentiating between UC and CD.[2,5]

Colonoscopy may aid diagnosis, determining the extent and severity of disease and for monitoring disease activity (although it should not be used routinely in severe disease because of the perforation risk).[2] In long-standing disease, colonoscopy with multiple biopsies is used for dysplasia and cancer surveillance. The typical endoscopic finding in UC is continuous, diffuse inflammation that almost always involves the rectum. Depending on disease severity, findings will range from erythema, edema, and a "sandpaper" appearance (mild disease), to a superficially denuded and eroded appearance with diffuse friability and mucopurulent exudates (moderate disease), to marked inflammation, gross ulceration, and spontaneous bleeding (severe disease). In CD, endoscopic findings are highly variable. Hallmarks of Crohn's colitis include a focal and segmental distribution of aphthous, irregularly shaped or linear ulcers, and a "cobblestone" appearance interspersed with normal-appearing mucosa. The rectosigmoid appears normal in 50% of patients. Findings characteristic of UC or CD are less reliable when IBD is chronic or severe or if endoscopy is performed following successful treatment.[2]

Morphologic criteria have been developed to distinguish UC, CD, and other forms of colitis.[6] Typical features in UC include crypt abscesses with neutrophil accumulation; an irregular, villous mucosal surface; decreased mucus content; and crypt distortion or atrophy.[2] Barium studies are useful for distinguishing UC and CD. Small-bowel radiograms typically are normal in UC. In contrast, 75% of CD patients have some small-bowel involvement. Barium enema studies in UC patients show characteristic symmetric, contiguous involvement and pseudopolyposis. In CD, findings include asymmetry, skip areas, serpiginous ulcerations, transverse fissures, and fistulae. Strictures are more common in CD than in UC, where they are more likely to signal malignancy. Noncaseating granulomas are virtually diagnostic of CD but are seen in only 10% to 28% endoscopic biopsies and half of surgical specimens. Microgranulomas and giant cells also are associated with CD.[2]

The diagnostic workup for this patient revealed moderately active UC with proctosigmoiditis extending 28 cm. What are the treatment options?

Treatment of UC is based on the site and severity of disease,[7] and because this patient's inflammation is distal (limited to below the splenic flexure), it is within the reach of topical therapy with 5-aminosalicylic acid (5-ASA) or corticosteroids. Distal UC also may be treated with oral 5-ASAs. Indeed, oral 5-ASAs are effective in the treatment of mildly to moderately active UC whether patients have pancolitis, left-sided disease, or distal disease.[8] The delivery system that is used, therefore, is largely determined by patient preference.[7]

Topical treatment — The vehicle for topical treatment for the patient in this case is guided by the proximal extent of disease. Enemas, because they reach farther than either suppositories or foams (suppositories and foams reach 15 to 20 cm),[7] would be the best option for this patient.

State of the Art in the Management of Inflammatory Bowel Disease: A Case Studies Newsletter is the fourth in a series of newsletters based, in part, on the proceedings of a roundtable that was held in Washington, DC. Although discussions at the roundtable covered the spectrum of management issues in inflammatory bowel disease, each newsletter expands on topics of particular importance or explores treatment issues using a case-presentation approach. Learning objectives of that roundtable were as follows:

By the end of the program, participants were able to discuss what was known about sex differences and to summarize current findings and identify knowledge gaps as they apply to the:

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with inflammatory bowel disease (IBD)
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Psychosocial challenges IBD patients face
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

STATEMENT OF NEED: IBD afflicts approximately 1 million Americans, and many patients suffer a complex spectrum of symptoms and complications across the lifespan. Fortunately, strategies for the management of IBD continue to evolve as the result of research advances, growing clinical experience, and an expanding therapeutic armamentarium. An appreciation of the clinical challenges of IBD is critical to developing appropriate therapeutic regimens that can positively impact the many disease presentations. Key aspects of patient management require knowledge of the epidemiology and proposed etiologies of IBD; diagnostics findings in adults and children; how to successfully integrate traditional and new therapies for inducing and maintaining remission; approaches for managing disease relapse and progression; treating the potentially debilitating extraintestinal manifestations that afflict approximately 25% of patients;[1] key strategies for improving medication adherence; and the impact of disease on childhood and pregnancy. These and other issues are addressed in this newsletter.

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Please direct all correspondence to:
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Generic Name	Trade Name	Approved Use (if any)	Unapproved/ Investigational Use
Azathioprine (derivative of 6-mercaptopurine)	Imuran®	Rheumatoid arthritis and renal transplantation	Crohn's disease and ulcerative colitis
Budesonide	Pulmicort Turbuhaler®, Rhinocort®	Asthma and allergic rhinitis	N/A
	Entocort™	Crohn's disease	
Ciprofloxacin	Cipro®	Various aerobic bacterial infections	Crohn's disease
Cyclosporine	Sandimmune®, Neoral®	Allogeneic transplantation, rheumatoid arthritis, and psoriasis	Crohn's disease and ulcerative colitis
5-Aminosalicylate mesalamine	Asacol®, Pentasa®, Rowasa®, Canasa®	Ulcerative colitis	Crohn's disease
olsalazine sodium	Dipentum®		
balsalazide disodium	Colazal™		
Glucocorticoids (hydrocortisone, prednisone, and prednisolone)	Various	Ulcerative colitis and numerous other indications	N/A
Infliximab (anti-TNF-α monoclonal antibody)	Remicade®	Moderately to severely active Crohn's disease refractory to conventional treatments, fistulizing Crohn's disease, and rheumatoid arthritis	Ulcerative colitis and other inflammatory disorders
Methotrexate	Various	Neoplastic disease, psoriasis, and rheumatoid arthritis	Crohn's disease, ankylosing spondylitis, primary sclerosing cholangitis
6-Mercaptopurine	Purinethol®	Chemotherapy, leukemia, and transplantation	Crohn's disease and ulcerative colitis
Metronidazole	Flagyl®	Trichomoniasis *(Trichomonas vaginalis),* amebiasis, and anaerobic bacterial infections	Crohn's disease
Nicotine		N/A	Ulcerative colitis
Sulfasalazine	Azulfidine®	Ulcerative colitis	Crohn's disease
Tacrolimus	Prograf®	Allogeneic transplantation	Primary sclerosing cholangitis, Crohn's disease, ulcerative colitis
	Protopic®	Atopic dermatitis	
Thalidomide	Thalomid™	Erythema nodosum leprosum	Crohn's disease

TNF=tumor necrosis factor; N/A=not available

A meta-analysis and literature review compared the effectiveness of various treatments, including topical mesalamine and corticosteroids in active and quiescent left-sided UC and ulcerative proctitis.[9] Pertinent to the patient in this case, the meta-analysis found that mesalamine enemas and suppositories were associated with higher clinical remission rates than were steroid-based enemas. Remission rates with mesalamine suppositories were similar to those with mesalamine enemas and also were higher than with steroid-based treatment. Mesalamine exhibited a duration but not a dose effect — remission rates increased with longer treatment.[9]

Oral 5-ASAs — The available 5-ASAs include delayed-release and sustained-release mesalamine preparations and various mesalamine prodrugs, including sulfasalazine, olsalazine, and balsalazide. A recent review of the pharmacokinetic profiles of these oral agents indicated that systemic exposure is comparable for all formulations, so selection of therapy should be based on factors such as efficacy, dose response, toxicity of the parent compound and metabolites, adherence issues relating to dose forms and dosing schedules, and cost.[10]

The first 5-ASA to be developed was sulfasalazine. It is cleaved by intestinal flora in the colonic lumen into sulfapyridine and its active moiety, 5-ASA.[11] Clinical improvement or remission of mild to moderate UC is achieved with sulfasalazine at dosages of 2 to 6 g/day, with greater efficacy at dosages higher than 3 g/day.[11] Side effects, mainly due to the therapeutically inactive sulfapyridine moiety, are common and increase as the dose is increased, thus limiting the use of higher, more effective doses.[11] Oral 5-ASAs are effective at dosages ranging from 1.5 to 4.8 g/day. The response to mesalamine is dose related, with improved responses at doses above 2 g/day.[11] Unlike with sulfasalazine, mesalamine side effects do not increase when mesalamine doses are increased.[11] Indeed, the side-effect rate of mesalamine is similar to that of placebo. In a meta-analysis of 3 trials comparing 5-ASAs with placebo in the treatment of UC, more placebo-treated patients (33%) than 5-ASA treated patients (31%) experienced side effects.[12] All of the available 5-ASA agents have similar clinical efficacy when equimolar concentrations are used.[11] There is no definitive evidence of efficacy differences between the various 5-ASA formulations for treatment of pancolitis, left-sided disease, proctosigmoiditis, or proctitis.[11]

Combined oral and topical mesalamine — A third treatment option for this patient is combined oral and topical mesalamine. Safdi and colleagues examined the efficacy of oral mesalamine (2.4 g/day), a once-nightly mesalamine rectal enema (4 g), or combined treatment in a double-blind trial involving 60 patients.[13] Combined treatment produced greater improvement (percentage of patients reporting no rectal bleeding over time) than did oral or rectal therapy alone. This difference was statistically significant in comparison with oral therapy alone.[13] Although combined treatment was more effective than either treatment alone, the authors suggested that the superior efficacy may have been due to the higher cumulative dose of mesalamine that was achieved when patients used both therapies.[13] Therefore, an important clinical point regarding mesalamine therapy is to use maximal doses to ensure optimal benefit.

Induction therapy was successful, and the patient has achieved remission. What are the options for maintenance therapy?

Oral or topical 5-ASAs are the mainstays of maintenance therapy in UC. Both routes of delivery are effective, and thus the choice is driven by

patient preference. Often, the need for nightly enemas becomes an adherence or quality of life issue for patients, but it may be possible to maintain remission using mesalamine enemas (1 to 4 g) on alternate nights or nightly enemas for 1 week per month.[11] If this patient prefers the oral route, she can be maintained successfully on oral 5-ASAs provided the dose is high enough. In the past, for patients who had achieved remission using sulfasalazine, the suggested maintenance dosage was 50% of the induction dosage. This approach was based not on efficacy, but on this agent's toxicity at higher doses. Because there is no dose-related toxicity associated with mesalamine, the current recommendation is to use the identical mesalamine dosage for maintenance that was used to achieve remission.[4] Combined oral/topical treatment also is very effective. d'Albasio and coworkers found that 1 year of treatment with 5-ASA 1.6 g/day and 5-ASA enemas twice per week was more effective than oral therapy alone in preventing relapse (Figure 1).[14] In this study, intermittent enema therapy was well accepted, and it may be a particularly good approach for patients with a high risk of relapse.[14]

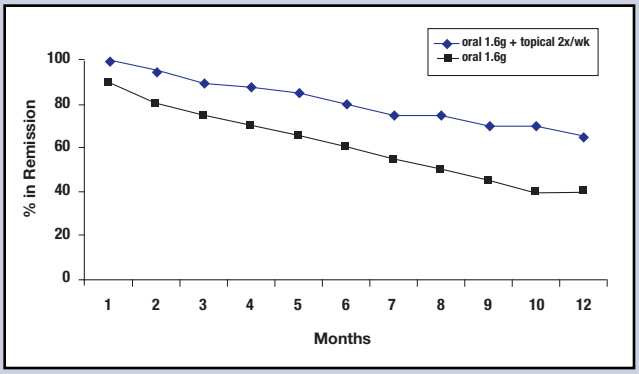
After 3 years in remission, this patient stopped taking all of her medications. Now, 8 months later, she presents with similar symptoms. Colonoscopy reveals that disease extends to the midtransverse colon. How should she be treated now?

After relapsing, this patient's UC has progressed to left-sided disease extending to the midtransverse colon, and she now requires more extensive therapy. Because her disease has similar severity to that at her initial presentation, she can receive first-line treatment with oral 5-ASAs, as has been discussed previously. Should she fail to respond to optimized oral and rectal 5-ASA therapy at adequate doses, oral corticosteroids should be initiated. Clinical improvement or remission can be achieved with prednisone or methylprednisolone 40 to 60 mg/day.[11]

Assuming the patient in this case was able to achieve remission of left-sided disease using 5-ASAs, she should then be maintained in remission at the same dosage used for induction. However, if she did not respond to optimal doses of 5-ASAs and corticosteroid therapy was initiated, maintenance treatment requires steroid tapering. Corticosteroids are ineffective as maintenance therapy.[11] For patients who are corticosteroid dependent or resistant, azathioprine (AZA) and 6-mercaptopurine (6-MP) have been used successfully to taper them off corticosteroids and to maintain remission.[11,15]

FIGURE 1

MAINTENANCE OF REMISSION IN UC WITH COMBINED ORAL AND TOPICAL MESALAMINE VS ORAL ALONE



Adapted with permission from d'Albasio G, et al. *Am J Gastroenterol*. 1997;92:1143-1147.

An 11-year-old boy presents with upper abdominal pain and weight loss but no significant diarrhea. His growth rate has slowed, and his height has dropped from the 75th percentile to the 50th percentile. He has a fever and an ESR of 100. What is the diagnostic workup?

For approximately 15% of patients with UC and CD, illness arises before the age of 20.[16] Pediatric IBD is especially challenging, because children have unique presentations and specific issues that add several important elements to their care. The key points are to achieve an early, accurate, and noninvasive diagnosis and then to manage not just the disease but any nutritional complications, adherence issues, and psychosocial aspects particular to this patient population.

Diagnostic approach — The diagnostic methods and criteria for children are the same as for adults, with the caveats that patients with pediatric onset have the unique features of growth failure and delayed sexual maturation (especially in CD), and that children present more with weight loss and fever than do adults.[17] The diagnosis is reached through a thorough history and physical examination combined with laboratory, endoscopic, histologic, and radiologic evaluations. Because of the invasiveness of the traditional approach, if the clinical suspicion of disease is low, the evaluation may be limited to ensuring a normal physical examination with no perianal disease and verifying normal growth velocity and can include limited laboratory testing (complete blood count, erythrocyte sedimentation rate, serum albumin, iron, and serologic testing for pANCA and ASCA). If the clinical suspicion is high, a full evaluation, as detailed in Table 1, should be performed.[17]

Diagnostic dilemmas — In most cases, children with UC present with diarrhea and rectal bleeding,[17] which generally leads to a rapid evaluation and diagnostic colonoscopy. In contrast, pediatric CD frequently has an insidious onset, with nonspecific symptoms such as nausea, vomiting, anorexia, weight loss, growth failure, pubertal delay, or peripheral arthritis.[17] These symptoms often delay the diagnosis because of overlap with bowel disorders such as recurrent abdominal pain or constipation, or they may be confused with anorexia nervosa or juvenile arthritis.

Thus, because of the invasiveness of traditional diagnostic testing, the nonspecificity of symptoms in some patients, and the need for an early, accurate diagnosis, researchers have looked for noninvasive tools to aid in diagnosis. Recent studies suggest that serologic testing for pANCA and ASCA may be useful in this regard.[18,19] Dubinsky and coworkers devised a novel diagnostic strategy for patients presenting with nonspecific symptoms that incorporated early, sequential serologic testing for pANCA and ASCA. The overall accuracy of this algorithm was 84%, and it reduced false-positive diagnoses by 81%, thus enabling avoidance of unnecessary invasive testing in children without IBD.[19] Ruemmele and colleagues assessed the accuracy of IgA and IgG ASCA

TABLE 1

EVALUATION OF THE CHILD WITH SUSPECTED IBD

History
- Abdominal pain, appetite
- Stool frequency, consistency, rectal bleeding, nocturnal diarrhea
- Family history: affected members, familial growth patterns
- Previous growth data
- School attendance and daily activity
- Psychosocial history, including impact on daily life of patient and parents

Physical examination
- Height, weight
- Abdominal tenderness, mass
- Rectal examination; perianal disease
- Rash, arthritis, clubbing, oral lesions
- Anthropometry/Tanner staging

Laboratory tests
- CBC, ESR
- Serum total protein; albumin; iron; calcium; magnesium; folate; vitamins A, E, B_{12}; zinc
- Stool guaiac, leukocytes, urinanalysis
- Stool bacterial culture, smears for ova and parasites, *Clostridium difficile* toxin assay
- Additional tests as indicated: pANCA, ASCA, lactose/glucose breath-H_2 test for lactose intolerance/bacterial overgrowth, 72-h fecal fat quantitation, stool alpha-1-antitrypsin

Radiographic studies
- Upper gastrointestinal and small-bowel series
- Bone age
- Additional tests as indicated: abdominal plain films, enteroclysis, fistulogram, ultrasound and CT scan with contrast medium, hexamethylpropyleneamine oxime-labeled white blood cell scan

Endoscopic studies
- Colonoscopy (with ileoscopy) with biopsies
- Upper endoscopic biopsies and endoscopic retrograde cholangiopancreatography (if indicated)

Adapted with permission from Shashidhar H, et al. In: Kirsner JB, ed. *Inflammatory Bowel Disease.* Philadelphia, Pa; WB Saunders Company; 2000:326-334.

and pANCA titers in pediatric patients with UC, CD, or non-IBD. IgA and IgG ASCA titers were significantly higher and highly specific for CD, and pANCA was specific for UC and absent in all non-IBD controls.[18] The researchers concluded that combined use of these assays is helpful in the diagnosis of IBD. Although serologic studies may point to a diagnosis of IBD, subsequent confirmation procedures are necessary to define the disease location, its extent, and the presence of complications (strictures, fistulae, abscesses, etc).

The patient in our case has abdominal pain, the most common symptom in pediatric patients with CD. Frequently, pain begins with meals and is cramping in nature. Growth failure is also common in CD; nearly half of pediatric patients present with this feature.[20] This patient also presented with fever; other common symptoms of CD include diarrhea, rectal bleeding or hematochezia, and arthritis/arthralgia.[17]

Further evaluation establishes that this patient has moderate to severe CD. How should I treat him?

Medical treatment of children with CD, as of adults, is based on the site and severity of disease. Table 2, page 6, provides a list of agents and dosages. Treatment goals are to induce and maintain remission, minimize side effects and long-term complications, and optimize nutritional status. Treatment options for children with CD generally are the same as for adults, although there is increased emphasis on avoiding systemic corticosteroid therapy; as steroids are associated with bone disease and impaired growth, compounding complications already faced by CD patients.

Aminosalicylates — 5-ASAs are first-line therapy for mild to moderate CD. Both sulfasalazine and mesalamine are effective, although mesalamine is associated with fewer side effects. Barden and coworkers compared side effects of sulfasalazine and mesalamine in 67 children with quiescent UC, CD, or indeterminate colitis. Patients received sulfasalazine 250 mg tid to 1000 mg qd or mesalamine 400 mg qd to 800 mg bid.[21] Although both agents were equally effective in remission maintenance, patients experienced fewer side effects with mesalamine than with sulfasalazine. Severe adverse events were reported in 3 children taking sulfasalazine and none taking mesalamine.[21] Further, among 45 patients switched from sulfasalazine to mesalamine, 73% expressed a preference for mesalamine because of easier administration.[21] It is important to note the safety and good tolerability associated with mesalamine, given the relatively higher doses, on a body-weight basis, administered to children than to adults each day.

Corticosteroids — Corticosteroids are effective for inducing remission in moderate to severe CD, but corticosteroid use in children is particularly problematic. Decreased bone mineral density is a common complication of CD, and corticosteroid use is considered an important contributing factor.[22,23] Glucocorticoids are the most common cause of drug-induced osteoporosis; skeletal effects are related to both dose and duration of use.[24] Growth failure also may be complicated by corticosteroid use. Markowitz and colleagues found that adult CD patients with growth failure whose disease began during childhood or adolescence had used corticosteroids significantly longer than had CD patients who experienced normal growth.[22]

Budesonide is a newer corticosteroid with high topical activity but low systemic activity, and it was anticipated that this steroid would confer advantages over older agents regarding bone mineral density loss and growth delay. However, a recently published study showed that budesonide does not protect against bone loss and the potential for increased fracture risk.[25] Further, results of studies with pediatric CD patients treated with ileal-release budesonide suggested that it is also associated with subnormal growth.[26] The cumulative negative effects of corticosteroids have led some experts to suggest that they should be used with continued caution in treating pediatric patients with IBD.

AZA/6-MP — AZA and 6-MP are being used increasingly to induce and maintain remission in CD, and they appear to be particularly useful in eliminating or reducing steroid dependence.[27] Markowitz and colleagues recently reported a multicenter, placebo-controlled trial with 55 children with CD randomized to receive 6-MP and prednisone or prednisone

TABLE 2

DRUG DOSAGES FOR TREATING CHILDREN WITH CD

Agent	Dosage	Comments
Sulfasalazine	Initial: 25-50 mg/kg/d; increase to 75 mg/kg/d (maximum 4 g/d) if needed	Dose-limiting side effects; folate supplementation at 0.4-1.0 mg/d
Mesalamine	30-60 mg/kg/d (maximum 4.8 g/d)	No dose-limiting side effects at maximum dose
Corticosteroids	Prednisone equivalent 1.0-2.0 mg/kg/d IV or PO in 1-2 doses/d (maximum 60 mg/d)	Avoid if possible
Metronidazole	10-15 mg/kg/d (maximum 1 g) in 2-3 divided doses	
Ciprofloxacin	250-750 mg bid	Dosage depending on age and severity
Azathioprine	1.5-2.0 mg/kg/d	Monitoring of hematologic and hepatic function required; advise patients about symptoms of pancreatitis
6-Mercaptopurine	1.0-1.5 mg/kg/d	Monitoring of hematologic and hepatic function required; advise patients about symptoms of pancreatitis
Methotrexate	Initial: 5 mg/wk; increase at 2-4 wk intervals to maximum of 20 mg/wk	For highly selected patients; monitoring of hematologic and hepatic function required; advise patients about symptoms of pancreatitis
Cyclosporine	Initial: 4 mg/kg/d, continuous or divided, q12h PO; maintenance 3-5 mg/kg bid	For highly selected patients
Infliximab	5 mg/kg IV infusion	Further assessment necessary

Serrano MS, et al. *Ann Pharmacother.* 2001;35:823-828. Kirschner BS. In: Kirsner JB, ed. *Inflammatory Bowel Disease.* Philadelphia, Pa; WB Saunders Company; 2000:578-597.

alone. Treatment was continued for 18 months.[28] For patients receiving 6-MP, the duration of steroid use was significantly shorter, as was the cumulative steroid dose at 6, 12, and 18 months. Although both groups achieved remission at equal rates, patients treated with 6-MP plus prednisone were significantly less likely to relapse.[28] No clinically significant adverse events were noted with either treatment.[28] The safety and efficacy results of this trial support the use of AZA/6-MP for newly diagnosed patients with moderate-to-severe disease.

Antibiotics — The efficacy and safety of the antibiotics metronidazole and ciprofloxacin have been evaluated primarily in adults. Uncontrolled studies, retrospective analyses, and one placebo-controlled trial suggest overall clinical benefit.[29-32] Though these antibiotics may represent a promising option for patients with active, refractory disease,[33] further studies are needed before they can be used routinely.

Methotrexate — Methotrexate is a treatment option for carefully selected patients with severe disease for whom other immunomodulatory therapies fail. It was shown to be effective for adults with active CD in a randomized, double-blind, placebo-controlled trial.[34] Testing in pediatric patients has been limited. Further, methotrexate has numerous potential side effects; treatment must be monitored carefully, and there are several contraindications to therapy.[34]

Cyclosporine and tacrolimus — The clinical evidence for the use of cyclosporine by adults has been contradictory. Whereas one randomized study reported positive results,[35] subsequent trials did not show benefit with cyclosporine treatment,[36] likely because of the low dosages used in the trials. Data with children are limited. Cyclosporine should be used only for highly selected patients with severe, refractory disease for whom other treatments have failed. Similarly, the use of tacrolimus treatment for children has not been well studied. One open-label study reported efficacy in inducing, but not maintaining, long-term remission.[37]

Thalidomide — Data on the use of thalidomide in pediatric CD are limited to case reports and small, open studies. In the few reports available, thalidomide appears to induce remission and reduce steroid dosage for patients with severe, refractory CD.[38]

Infliximab — Infliximab is approved for treatment of active CD in adults. In pediatric patients, studies currently are limited to retrospective analyses. Two reports have indicated that infliximab treatment is associated with clinical improvement,[39,40] but further investigation into the efficacy, safety, and cost-effectiveness of this agent in the pediatric population is required.

Surgical management — The frequency of surgery in children with CD was reported as 79% in one study and 69% in another. Surgical indications in children with CD include disease refractory to medical treatment, suspected perforation or abscess, intestinal obstruction, hemorrhage, and growth failure.[41]

Nutritional intervention — Nutritional deficiencies arising from low calorie intake are common in children with CD. Most often, insufficient dietary intake is the culprit — patients eat inadequately because food

may exacerbate abdominal pain and diarrhea.[20] Nutritional supplementation, which is essential for most patients, is used to control disease activity, restore normal body composition, and reverse weight loss and growth failure. A review of the literature on the role of nutritional therapy found that elemental, semi-elemental, and polymeric diets are useful not only for nutritional support and for reversing growth failure but also for inducing remission in CD. Dietary therapy has been shown in several studies to be generally comparable to steroid treatment for remission induction.[20] This approach has the advantage of providing nutritional repletion with few or no side effects and avoiding steroid therapies that compound growth problems. However, there are several limitations: Patients with extensive or distal colonic involvement or who have severe anorectal disease often do not respond well. Further disadvantages include low palatability and the relatively high cost of diet therapy.[20]

Psychosocial aspects of pediatric CD — In addition to the spectrum of signs and symptoms of CD found in adults, children have the further difficulties of growth retardation and delayed puberty. Also, the limitations imposed by the disease on schooling, social life, and family life can be profound. In a study by Moody and colleagues, a majority of CD patients reported prolonged absences from school, unsympathetic treatment by teachers, and educational underachievement. Most were unable to participate in sports regularly, and 60% were unable to leave their homes at all. Children expressed concerns regarding sleeping over at friends' homes and going on vacation.[42] These negative effects on quality of life extend to the entire family. Parents may be concerned about medication side effects, the limitations their children currently face, their children's future, and missing days of work to care for their children.[43]

Gastroenterologists not only must control the disease medically but must make efforts to ensure good psychosocial functioning so that children with CD and their families can achieve the best possible quality of life. IBD is a lifelong disease, and its treatment during childhood is key to future development and success.

Your 29-year-old female patient with Crohn's ileitis has been successfully maintained on mesalamine 4.8 g/day for the past 6 months. She recently discovered that she is pregnant and is concerned about the effects of treatment on her developing baby. How should she be counseled?

Although it is normal that your patient be concerned regarding the safety of medication taken during pregnancy, it is essential that she continue her treatment regimen. Remission maintenance is the greatest investment for a favorable pregnancy outcome, because the greatest risk to pregnancy is active disease, not IBD therapy.[44]

Pregnancy itself appears to have little effect on disease status. Pregnant women with quiescent CD are no more likely to relapse during pregnancy and for 3 months postpartum than would be nonpregnant women over the same period. In pregnant women with active disease, CD tends to stay the same in one third of cases, improve in one third, and worsen in one third.[45] The effect of CD on pregnancy and the developing fetus is relatively minimal as well, provided the disease is in remission. If remission can be maintained for the patient in this case, she can be assured that pregnancy is safe and the outcome should be excellent. In contrast, active disease has negative effects on pregnancy outcomes. There is an increased risk of spontaneous abortion, stillbirth, or premature delivery.[45] A recent cross-sectional retrospective study determined that infants born to mothers with CD were more likely to be preterm, have low birth weights, and be small for gestational age.[46] Although these data must be interpreted with caution, since the medical histories of the mothers were not known, they do underscore the need for careful monitoring and treatment of the patient during pregnancy. The treatment imperative is to maintain the same regimen throughout pregnancy to avoid relapse and to maximize the pregnancy outcome.

This patient is taking mesalamine, which is a category B agent and can be considered safe for use during pregnancy. In a prospective, controlled cohort study, pregnancy outcomes for 165 women exposed to mesalamine during pregnancy were compared with those of a matched control group (Table 3). There were no significant differences between groups in maternal obstetric history, rates of live births, miscarriages, pregnancy terminations, ectopic pregnancies, delivery methods, or fetal distress. Further, mesalamine was not associated with malformations; major malformations occurred in 0.8% of infants in the treatment group versus 3.8% of infants in the control group.[47] In this study, 20% of women were taking a mean daily dose of 2.4 to 3.2 g, and another 20% were taking dosages of at least 3.2 g/day, which suggests that higher dosages are safe during pregnancy.[47] Your patient should be maintained on the same dosage, 4.8 g/day, that she was taking before she became pregnant.

TABLE 3
PREGNANCY OUTCOMES WITH MESALAMINE

	Mesalamine	Control	*P* value
Pregnancy outcome (%)			
Live birth	88.5	89.7	.41
Spontaneous abortion	6.7	8.5	
Therapeutic abortion	4.2	1.8	
Ectopic pregnancy	.6	0	
Major birth defects (%)	.8	3.8	.21
Minor birth defects (%)	6.3	3.8	.56
Delivery method (%)			
Vaginal/vertex	79.5	76.4	.91
Vaginal/breech	1.4	2.0	
Elective Cesarean section	6.2	7.4	
Emergency Cesarean section	13.0	14.2	
Gestational age (wk) (mean ± SD)	39.2 ± 2.1	39.6 ± 1.5	.08
Preterm delivery at <37 wk (%)	13.0	4.7	.02
Birth weight (g) (mean ± SD)	3253 ± 546	3461 ± 542	.0005

Adapted with permission from Diav-Citrin O, et al. *Gastroenterology*. 1998;114:23-28.

The patient elected to stop her medications, because she was fearful that any medications during pregnancy would be harmful. She's now in her fifth month and has begun to have severe right-sided abdominal pain, chills, and fever. She is anemic. How do you treat this patient? Do you put her back on mesalamine? Initiate corticosteroids? AZA/6-MP?

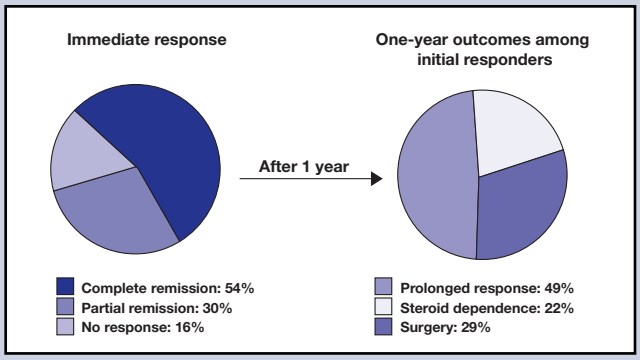
This patient is now presenting with disease relapse, with severe systemic symptoms and risk to her pregnancy. Under these circumstances, aggressive treatment is necessary. Mesalamine is not likely to control the more severe symptoms, so other treatment options should be explored. Corticosteroids, metronidazole and ciprofloxacin, AZA/6-MP, and infliximab are among the available options; methotrexate use is contraindicated.[48] Few controlled studies have evaluated the effects of these agents on the developing fetus, and most of the available evidence comes from animal studies, case reports, and retrospective analyses.

Corticosteroids, metronidazole, and infliximab are classified as category B agents in pregnancy, meaning either that animal studies have not shown a risk to the fetus and there are no controlled studies with pregnant women or that animal studies do indicate a fetal risk but controlled studies with women do not. Although several reports have suggested that corticosteroids are associated with stillbirth or low birth weight, the majority have shown no evidence of fetal harm.[45] Metronidazole is considered safe to use after the first trimester.[48] Infliximab, also in this category, is relatively new, and little is known about how it may affect fetal outcome. Though it is premature for infliximab to be used routinely, the risk:benefit ratio may favor its use for the patient in this case.

Ciprofloxacin and cyclosporine are in category C. Either animal studies have shown a fetal risk and there are no controlled studies with women or there are no available studies with women or animals.[48] One review of ciprofloxacin use in pregnancy reported a range of adverse events. Among 103 women exposed during the first trimester, there were 63 normal births, 18 therapeutic abortions, 10 spontaneous abortions, 8 congenital abnormalities, and 4 fetal deaths in utero.[49] These data suggest that it should be used with caution and only when there is a significant need. Similarly, there are few available data on the use of cyclosporine. Based on a small number of reports, it does not appear to pose a major risk to the fetus.[48]

AZA and 6-MP are classified as pregnancy category D agents, meaning that there is positive evidence of fetal risk. Although AZA and 6-MP are effective and generally safe, the data are conflicting in regard to their use during pregnancy. Most of the available evidence of their effects on pregnancy outcomes is from their use in renal transplant patients.[50] For pregnant women with renal allografts who were taking AZA/6-MP, 80% to 90% of gestations that continued beyond the first trimester were successful. No frequent or predominant congenital abnormalities have been noted.[50] The safety of 6-MP for child-bearing patients was evaluated in a case-controlled study among 155 patients with IBD who had been exposed to 6-MP. Some patients had conceived after stopping 6-MP, some had conceived while taking 6-MP and had stopped during pregnancy, some had conceived while taking 6-MP and continued through pregnancy, and some had conceived prior to ever taking 6-MP. Treatment was not associated with increased prematurity, spontaneous abortion, congenital abnormalities, or childhood infections or neoplasia.[51] Thus, under certain circumstances, the benefit of AZA/6-MP might outweigh the risk. One caveat to its use in this case, however, is the relative interval (approximately 3 months) required before benefits are attained.

FIGURE 2
NATURAL HISTORY OF CORTICOSTEROID USE IN ULCERATIVE COLITIS



Faubion WA Jr, et al. *Gastroenterology.* 2001;121:255-260.

You chose to hospitalize the patient and initiate IV corticosteroids. She responded to a 10-day course and was tapered from steroids as mesalamine was reinitiated and titrated up to 4.8 g/day. The patient delivered at 37 weeks. Although the baby was small for gestational age, he was otherwise healthy. Should your patient breast-feed?

Information on the effects of IBD medications during breast-feeding is limited, although several agents, such as mesalamine, sulfasalazine, and corticosteroids, are considered to be safe. Because the patient in this case was tapered from steroids and is once more taking mesalamine, she can be assured that it is safe to breast-feed and continue treatment.[48]

Because addition of AZA/6-MP may further improve remission maintenance, it also may be considered for this patient.[27,52] However, there is little available information on the use of AZA/6-MP while breast-feeding, and some experts suggest that it should only be used if clearly needed. Regarding other drugs used in remission maintenance, few data exist regarding the use of infliximab while breast-feeding, and metronidazole and ciprofloxacin should be avoided if possible.[48] Methotrexate and cyclosporine are contraindicated for nursing mothers.[48]

A final consideration is the effect of breast-feeding on CD activity. Women with rheumatoid and inflammatory arthritis have been reported to experience disease flares during breast-feeding.[53] Whether women with CD also are at increased risk of relapse if they breast-feed is an area requiring further research. The decision to breast-feed is a highly personal one. Should the patient in this case decide to breast-feed, a

careful assessment must be made of the risks and benefits of the available treatment options so that an optimal balance can be achieved for the health of both mother and child.

Your 30-year-old male patient (an ex-smoker) with a 3-year history of pancolitis achieved remission following a 9-week course of corticosteroids. How would you maintain remission in this patient?

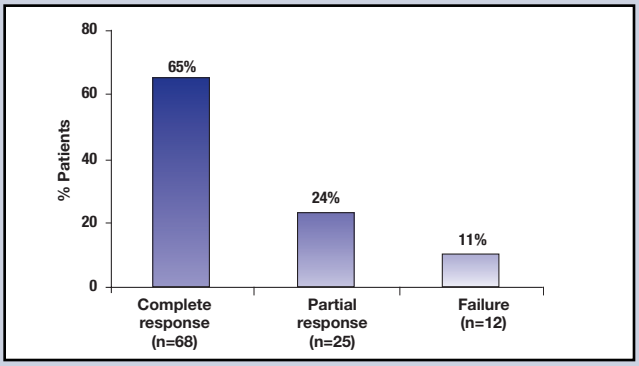
This patient presented with more severe disease at the onset, and remission was induced successfully with a course of corticosteroid treatment. The next step is to manage the transition to maintenance therapy, which requires that several key principles be borne in mind. First, complete remission must be achieved before a patient can begin maintenance therapy — if remission is not attained, maintenance therapy will be compromised.[4] Second, maintenance therapy must be highly individualized based on the extent of disease, the type and intensity of induction therapy used, and the response to prior treatment (history of relapse, adherence issues). Third, maintenance therapy should not be withdrawn, and it is essential that the patient be educated that relapse can occur if dosages are reduced or treatment is stopped.[4]

For a steroid-treated patient, it is essential to taper corticosteroids, which typically is done according to the rate at which remission was achieved, not mistaking corticosteroid dependency for a maintenance effect. Steroid-dependent patients initially respond to corticosteroids, but they relapse when steroids are tapered or shortly after discontinuation; these patients require re-initiation of steroid therapy to maintain symptom control.[4]

Because of its inefficacy as maintenance therapy, the phenomena of steroid dependence and resistance, and a wide range of short- and long-term side effects, some opinion leaders counsel the avoidance of corticosteroid therapy altogether. Support for this view has been provided by Faubion and colleagues, who studied the outcomes of initial steroid use by 63 UC patients (Figure 2). Immediate outcomes were complete remission in 54% of patients, partial remission in 30%, and no response in 16%.[54] Of the 10 patients (16%) who were steroid resistant, 9 underwent colectomy after a median of 33 days.[54] Steroid-nonresponsiveness was a surrogate marker for surgery. At 1 year, of the patients who initially responded (either completely or partially), only 49% had maintained remission. Twenty-two percent were steroid dependent, and 29% required surgery. Overall, even among those patients who did respond initially to treatment, corticosteroid use was found to be a marker of poor prognosis.[54]

FIGURE 3

6-MP TREATMENT IN CHRONIC, REFRACTORY UC



George J, et al. *Am J Gastroenterol.* 1996;91:1711-1714.

Treatment sequences for induction and maintenance therapy — UC is a disease that is managed sequentially, first by achieving remission and then by maintaining it. The choice of agent used first in this sequence depends on the extent and severity of disease, and the choice of agent for maintenance depends on the treatment used for induction. Most pertinent to this patient in this case is the approach to maintenance therapy when remission is attained with corticosteroids. Because corticosteroids are ineffective for maintenance therapy, they must be tapered. Traditionally, patients have been tapered to 5-ASAs. Often, corticosteroid-treated patients are concomitantly taking 5-ASAs, which should be optimized to 4.8 g/day. For patients not taking 5-ASAs, treatment should be initiated and dosages titrated up to optimal dosage. Once adequate dosage levels of the 5-ASA are achieved, corticosteroid tapering can begin.[4] Whether 5-ASAs alone are sufficient after corticosteroids is an issue that requires further clinical investigation. Addition of AZA/6-MP may improve results and may be particularly useful when patients are steroid dependent (Figure 3).[27,52]

For this patient, maintenance therapy (mesalamine 2.4 g/day) was initiated and steroids were tapered. He presents today with significant weight loss, bloody diarrhea, fever, anemia, and abdominal pain. What is your course of treatment now?

It is unlikely that the mesalamine dosage prescribed for this patient was high enough to maintain disease quiescence. Given the safety profile of high doses and the fact that efficacy is dose related, dosages of up to 4.8 g/day should be used. Another reason for this patient's current symptomatology is steroid dependency, as his symptoms reemerged when corticosteroids were tapered.

This patient is now presenting with extensive, severe UC. It is still possible to treat him on an outpatient basis if you know he will adhere to treatment, is able to maintain close contact with you, and has a supportive home environment.[4] Among the treatment options are reinitiation of oral corticosteroids with maximization of the 5-ASA dosage to 4.8 g/day. Once remission is reestablished and optimal 5-ASA doses attained, the steroid should be tapered. If steroid tapering again leads to relapse, steroid dependence should be suspected. If this is the case, treatment with AZA/6-MP should be initiated.[4]

The utility of AZA/6-MP therapy for patients taking steroids was investigated in a retrospective chart study. One hundred five patients with chronic, refractory UC were treated with 6-MP starting at 50 to 60 mg/day, and followed for a mean of 5 years.[27] A complete response was defined as the ability to discontinue oral steroids and to have no more than 3 formed, nonbloody bowel movements daily. A partial response was a 50% reduction in prednisone dose, a daily dose of

prednisone lower than 15 mg, and no more than intermittent diarrhea (with or without bleeding). Failure was defined as the inability to decrease steroids without continuous symptoms.[27] Sixty-five percent of patients were able to discontinue steroid treatment completely (Figure 3, page 9). Although 35% of patients who had achieved complete remission later relapsed, complete remission was restored in 88%, with more than half not requiring additional steroid treatment.[27]

Another potential option for this patient is smoking resumption. An epidemiologic relationship between UC and smoking has long been appreciated. Both active and passive cigarette smoking have a protective effect on the risk of UC, and the cessation of smoking can aggravate UC.[55,56] The inverse association between smoking and UC has led to several randomized trials assessing the effect of nicotine gum or patches on active or quiescent UC. The data thus far suggest that nicotine may have a modest benefit for some patients[57] and may be useful as adjunctive therapy in conjunction with conventional agents.[58] The balance between health and UC may favor short-term resumption of smoking in a certain subset of patients with severe disease for whom the risk:benefit ratio is carefully considered.

Oral corticosteroid treatment was reinitiated. Despite 2 weeks of outpatient treatment, however, the patient did not improve. What are the remaining treatment options?

Although outpatient treatment may be a reasonable approach for some patients, it is impossible if there is a rapidly deteriorating course or if the patient shows no improvement after several weeks.[4] Under these circumstances, it is necessary to hospitalize the patient. Although there have been few clinical trials with patients with severe or fulminant disease, intravenous (IV) steroids are considered the standard of care. If a patient does not respond within 7 to 10 days, IV cyclosporine is an alternative treatment. Total parenteral nutrition is generally not beneficial but may be supportive for patients with severe nutritional depletion.[7]

Although cyclosporine treatment is often administered only in specialized centers because of the careful monitoring required, there is growing evidence of its effectiveness in the setting of severe colitis. In a series of 42 patients who were treated with IV cyclosporine, Cohen and colleagues reported that 36 (86%) initially responded to treatment, and most (72%) of these patients were able to avoid surgery. In contrast, 6 (14%) of patients whose initial therapy failed required immediate colectomy. Ten patients who initially responded eventually required surgery; however, cyclosporine treatment allowed surgery to be delayed.[59] Adjunctive therapy with AZA/6-MP for patients initially responding to therapy was also associated with avoidance of colectomy.[59] Initial support for cyclosporine therapy was provided by Lichtiger et al. In a randomized, double-blind, placebo-controlled trial with 20 patients, 9 of 11 (82%) cyclosporine-treated patients responded within 7 days, in comparison with none of 9 placebo-treated patients.[60] Furthermore, in a comparison of IV cyclosporine and IV corticosteroids for 29 patients, 53% of corticosteroid-treated patients and 64% of cyclosporine-treated patients responded, with remission up to 12 months for 78% of cyclosporine and 37% of steroid responders.[61]

If a patient with severe UC is not responsive to other treatment options, surgery is indicated.[7]

The patient in this case responded to IV cyclosporine treatment and was discharged from the hospital. What are the options for maintenance of remission?

There is accumulating clinical evidence that AZA/6-MP is effective for maintaining remission in patients with severe UC. In their patients treated with IV cyclosporine, Cohen and colleagues found AZA/6-MP therapy for patients who had initially responded to be associated with avoidance of colectomy. Of 36 patients with initial response, 25 were treated with 6-MP and 11 were not. Eventual surgery was required by only 20% of 6-MP–treated patients. In contrast, nearly half (45%) of patients not receiving 6-MP required colectomy.[59] In another retrospective study, 56 steroid-resistant or steroid-dependent patients were treated with AZA and followed for a mean of 29 months. Sixty-four percent of patients achieved remission with complete elimination of steroids within 1 year. With 2 and 3 years of treatment, the rates were 66% and 69%, respectively. Further, the need for steroid consumption was reduced by about two thirds compared with the 2 years prior to initiation of AZA therapy.[52]

CONCLUSION

Each individual who presents with IBD brings a unique set of challenges to the physician — not only because of the need to assess the patient and determine appropriate treatment but also because of special considerations that must be addressed. Thus, patient care requires a synthesis of clinical knowledge with understanding of the aspects that are specific to different patient populations, such as children or women in their childbearing years. Although diagnosis and initial treatment may be straightforward, the lifelong course of the disease and the potential for relapse and disease progression mean that clinicians must be adept at choosing appropriate approaches as requirements change. As illustrated by the clinical scenarios explored in these cases, the evolving needs of patients through the course of treatment and across the lifespan demand careful integration of the art and science of medicine. A comprehensive approach will do much to relieve the burdens associated with IBD.

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1. Typical endoscopic findings in ulcerative colitis (UC) include:
   a. A "cobblestone" appearance
   b. Normal rectosigmoid, in approximately 50% of patients
   c. Aphthous, irregularly shaped, or linear ulcers
   d. All of the above
   e. None of the above

2. Serologic testing of pANCA and ASCA antibody titers is useful because:
   a. Testing may aid in the differential diagnosis between UC and CD.
   b. It establishes a diagnosis of UC or CD in the case of indeterminate colitis.
   c. At the present time, information gained from serologic testing of pANCA and ASCA is too nonspecific to be of value in the diagnosis of IBD.
   d. It rules out colitis due to infectious organisms.
   e. None of the above

3. Which of the following statements is NOT true regarding the topical treatment of distal UC?
   a. Suppositories and foams may be used when the proximal extent of the disease is no more than 10 to 20 cm.
   b. A higher dose and longer duration of topical mesalamine was found by Cohen and coworkers to improve the rate of remission.
   c. Steroid-based topical treatment was less effective than either mesalamine suppositories or enemas.
   d. All of the above statements are true.

4. Which of the following treatment strategies has NOT been shown to be effective for induction of remission in distal UC?
   a. Nightly steroid enema
   b. Daily mesalamine using either an oral or topical route
   c. Daily oral mesalamine combined with a nightly mesalamine enema
   d. Nightly mesalamine enema one week per month
   e. All of the above

5. Which of the following statements regarding diagnosis of pediatric inflammatory bowel disease (IBD) is true?
   a. If pediatric patients have nonspecific symptoms, then serologic testing of pANCA and ASCA titers should be used instead of the traditional approach to establish a diagnosis of UC or CD.
   b. To rule out IBD in a case where there is a low index of suspicion for disease, only a thorough physical, assessment of growth parameters, and laboratory studies need be performed.
   c. Approximately half of patients with UC and CD present with growth failure.
   d. Noninvasive tools for the diagnosis of pediatric IBD are needed because the false-positive rate is 81% in patients with nonspecific symptoms.

6. The results reported by Markowitz and colleagues regarding combined 6-MP and steroid treatment suggested that:
   a. Patients receiving combined treatment experienced a significantly shorter duration of steroid use, and a significantly lower cumulative steroid dose.
   b. Because of the cumulative negative effects on growth and bone health, pediatric CD patients should not be treated with corticosteroids.
   c. Pediatric CD patients treated with ileal-release budesonide experienced subnormal growth.
   d. While remission rates were equal in patients treated with 6-MP and steroids or steroids alone, patients receiving combined treatment were less likely to relapse.
   e. a. and d.
   f. All of the above

7. Which of the following statements regarding pediatric CD is true?
   a. The rate of surgery in pediatric CD patients is relatively high because most patients with CD are refractory to medical treatment.
   b. Malabsorption of nutrients is the major reason for nutritional deficiency in pediatric patients with CD.
   c. The overall burden of CD often is greater in pediatric patients in comparison to adults because of the added problems of growth failure and pubertal delay.
   d. Slowed growth and bone mineral density loss may be minimized or avoided with budesonide treatment.
   e. All of the above

8. Which of the following statements reflect the safety of IBD treatments during pregnancy and breast-feeding?
   a. A study by Diav-Citrin indicated that mesalamine treatment was not associated with increased rates of miscarriages, ectopic pregnancies, or major malformations.
   b. Maintenance of remission of CD during pregnancy is a key goal because active CD is a greater threat to a good pregnancy outcome than adverse effects related to IBD treatments.
   c. Methotrexate is contraindicated during pregnancy and in nursing mothers.
   d. Metronidazole, infliximab, and corticosteroids are classified as category B drugs.
   e. All of the above

9. Which of the following treatment options can be used to induce remission in severe UC?
   a. Intravenous cyclosporine
   b. AZA/6-MP
   c. High-dose mesalamine
   d. Nicotine patches
   e. All of the above

10. In a study of the natural history of corticosteroid use in UC patients, Faubion and colleagues found:
    a. Although complete or partial remission was initially achieved by approximately 60% of patients, by 1 year only half were still in remission.
    b. Steroid nonresponsiveness was closely correlated with the need for IV cyclosporine.
    c. Nearly one quarter of patients initially responding to steroid treatment were steroid dependent after 1 year.
    d. In patients who had a complete response to corticosteroid therapy, approximately 84% were in remission at 1 year.
    e. All of the above

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